

WHAT IS CLAIMED IS:

- 1                   1.       A composition of matter comprising a linked plurality of molecules  
2       which specifically bind to the mammalian target of rapamycin (mTOR).
- 1                   2.       A composition of matter as in claim 1, wherein the molecules are  
2       selected from the group consisting of rapamycin, rapamycin hybrids, CCI-779, RAD-001,  
3       SDZ Rad (Everolimus), FK506 (Tacrolimus), ASM 981 (Pimecrolimus), Wortmannin, and  
4       Tumistatin.
- 1                   3.       A composition as in claim 2, having from 3 to  $10^6$  molecules linked.
- 1                   4.       A composition as in claim 3, having from 5 to  $10^5$  molecules linked.
- 1                   5.       A composition as in claim 4, having from 7 to  $5 \times 10^4$  molecules  
2       linked.
- 1                   6.       A composition of matter as in any of claim 1, wherein the molecules  
2       are linked via attachment to a backbone.
- 1                   7.       A composition of matter as in claim 6, wherein the molecules comprise  
2       rapamycin molecules which have been derivatized with linking moieties and wherein the  
3       rapamycin molecules are covalently bound through the moieties to the backbone.
- 1                   8.       A composition of matter as claim 7, wherein the linking moieties are  
2       bound to the rapamycin molecules at sites which do not sterically interfere with the active  
3       sites of rapamycin so that rapamycin retains its activity when attached to the backbone.
- 1                   9.       A composition of matter as in claim 7, wherein the linking moieties are  
2       bound to the rapamycin molecules at sites which sterically interfere with the active sites of  
3       rapamycin so that rapamycin activity is inhibited while the rapamycin remains attached to the  
4       backbone and restored when the rapamycin is released from the backbone.
- 1                   10.      A composition of matter as in claim 6, wherein the backbone degrades  
2       under preselected conditions to release the rapamycin molecules.
- 1                   11.      A composition of matter as in claim 7, wherein the linking moieties  
2       lyse under preselected conditions to release the rapamycin molecules from the backbone.

- 1                   12.     A composition of matter as in claim 7, wherein the backbone  
2 comprises a poly (amino acid).
- 1                   13.     A composition of matter as in claim 12, wherein the backbone is  
2 polyaspartate, wherein rapamycin is covalently attached via an ester linkage between a free  
3 carboxylic acid on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.
- 1                   14.     A composition of matter as in claim 12, wherein the backbone is  
2 polylysine, wherein rapamycin is covalently attached via a heterobifunctional linker between  
3 a free thiol on the lysine to a free hydroxyl at position 42 of rapamycin.
- 1                   15.     A composition of matter as in claim 12, wherein the backbone is  
2 polylysine, wherein rapamycin is covalently attached via an amide-ester linkage between a  
3 free amine on the lysine to a free hydroxyl at position 42 of rapamycin.
- 1                   16.     A composition of matter as in claim 12, wherein the backbone is  
2 polylysine, wherein rapamycin is covalently attached via a disulfide linkage through a free  
3 thiol introduced to the rapamycin.
- 1                   17.     A composition of matter as in claim 6, wherein the backbone  
2 comprises polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to  
3 the PEG by ester linkages between free hydroxyls on the PEG and on the rapamycin.
- 1                   18.     A composition of matter as in any of claim 1, wherein the molecules  
2 are polymerized.
- 1                   19.     A composition of matter as in claim 18, wherein the molecules  
2 comprise rapamycin molecules which have been derivatized with linking moieties and  
3 wherein the rapamycin molecules are polymerized through the linking moieties.
- 1                   20.     A composition of matter as in claim 19, wherein the linking moieties  
2 are bound to the rapamycin molecules at sites which do not sterically interfere with the active  
3 sites of rapamycin so that rapamycin retains its activity when polymerized.
- 1                   21.     A composition of matter as in claim 19, wherein the linking moieties  
2 are bound to the rapamycin molecules at sites which sterically interfere with the active sites

3 of rapamycin so that rapamycin activity is inhibited while the rapamycin remains  
4 polymerized and restored when the rapamycin is released.

1                   22.     A composition of matter as in claim 19, wherein the linking moieties  
2 lyse under preselected conditions.

1                   23.     A composition of matter as in claim 19, wherein the linking moieties  
2 comprise ascorbic acid attached to the rapamycin molecules via an ester linkage.

1                   24.     An implantable prosthesis comprising:  
2 a structure having a surface; and  
3 linked pluralities of molecules which specifically bind to the mammalian  
4 target of rapamycin (mTOR) present on the surface.

1                   25.     An implantable prosthesis as in claim 24, wherein the structure  
2 comprises a vascular prosthesis or stent implantable in a blood vessel.

1                   26.     An implantable prosthesis as in claim 24, wherein the linked pluralities  
2 are covalently attached to the surface.

1                   27.     An implantable prosthesis as in claim 24, wherein the linked plurality  
2 of molecules comprise molecules which are selected from the group consisting of rapamycin,  
3 rapamycin hybrids, CCI-779, RAD-001, SDZ Rad (Everolimus), FK506 (Tacrolimus), ASM  
4 981 (Pimecrolimus), Wortmannin, and Tumistatin.

1                   28.     An implantable prosthesis as in claim 27, having from  $3$  to  $10^6$   
2 molecules linked.

1                   29.     An implantable prosthesis as in claim 28, having from  $5$  to  $10^5$   
2 molecules linked.

1                   30.     An implantable prosthesis as in claim 29, having from  $7$  to  $5 \times 10^4$   
2 molecules linked.

1                   31.     An implantable prosthesis as in any of claim 24, wherein the molecules  
2 are linked via attachment to a backbone.

1           32.     An implantable prosthesis as in claim 31, wherein the molecules  
2     comprise rapamycin molecules which have been derivatized with linking moieties and  
3     wherein the rapamycin molecules are covalently bound through the moieties to the backbone.

1           33.     An implantable prosthesis as claim 32, wherein the linking moieties  
2     are bound to the rapamycin molecules at sites which do not sterically interfere with the active  
3     sites of rapamycin so that rapamycin retains its activity when attached to the backbone.

1           34.     An implantable prosthesis as in claim 32, wherein the linking moieties  
2     are bound to rapamycin molecules at sites which sterically interfere with the active sites of  
3     rapamycin so that rapamycin activity is inhibited while the rapamycin remains attached to the  
4     backbone and restored when the rapamycin is released from the backbone.

1           35.     An implantable prosthesis as in claim 31, wherein the backbone  
2     degrades under preselected conditions to release the rapamycin molecules.

1           36.     An implantable prosthesis as in claim 32, wherein the linking moieties  
2     lyse under preselected conditions to release the rapamycin molecules from the backbone.

1           37.     An implantable prosthesis as in claim 32, wherein the backbone  
2     comprises a poly (amino acid).

1           38.     An implantable prosthesis as in claim 37, wherein the backbone is  
2     polyaspartate, wherein rapamycin is covalently attached via an ester linkage between a free  
3     carboxylic acid on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1           39.     An implantable prosthesis as in claim 37, wherein the backbone is  
2     polylysine, wherein rapamycin is covalently attached via a heterobifunctional linker between  
3     a free thiol on the lysine to a free hydroxyl at position 42 of rapamycin.

1           40.     An implantable prosthesis as in claim 37, wherein the backbone is  
2     polylysine, wherein rapamycin is covalently attached via an amide-ester linkage between a  
3     free amine on the lysine to a free hydroxyl at position 42 of rapamycin.

1           41.     An implantable prosthesis as in claim 37, wherein the backbone is  
2     polylysine, wherein rapamycin is covalently attached via a disulfide linkage through a free  
3     thiol introduced to the rapamycin.

1                   42.     An implantable prosthesis as in claim 31, wherein the backbone  
2 comprises polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to  
3 the PEG by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1                   43.     An implantable prosthesis as in any of claim 24, wherein the molecules  
2 are polymerized.

1                   44.     An implantable prosthesis as in claim 43, wherein the molecules  
2 comprise rapamycin molecules which have been derivatized with linking moieties and  
3 wherein the rapamycin molecules are polymerized through the linking moieties.

1                   45.     An implantable prosthesis as in claim 44, wherein the linking moieties  
2 are bound to the rapamycin molecules at sites which do not sterically interfere with the active  
3 sites of rapamycin so that rapamycin retains its activity when polymerized.

1                   46.     An implantable prosthesis as in claim 44, wherein the linking moieties  
2 are bound to the rapamycin molecules at sites which sterically interfere with the active sites  
3 of rapamycin so that rapamycin activity is inhibited while the rapamycin remains  
4 polymerized and restored when the rapamycin is released.

1                   47.     An implantable prosthesis as in claim 44, wherein the linking moieties  
2 lyse under preselected conditions.

1                   48.     An implantable prosthesis as in claim 44, wherein the linking moieties  
2 comprise ascorbic acid attached to the rapamycin molecules via an ester linkage.

1                   49.     A method for preparing a linked plurality of molecules which  
2 specifically bind to the mammalian target of rapamycin (mTOR), said method comprising:  
3 providing a backbone molecule; and  
4 binding the plurality of molecules to the backbone molecule.

1                   50.     A method as in claim 49, wherein the molecules are selected from the  
2 group consisting of rapamycin, rapamycin hybrids, CCI-779, RAD-001, SDZ Rad  
3 (Everolimus), FK506 (Tacrolimus), ASM 981 (Pimecrolimus), Wortmannin, and Tumistatin.

1                   51.     A method as in claim 50, wherein the plurality consists of from 3 to  
2  $10^6$  molecules.



1                    52.     A method as in claim 51, wherein the plurality consists of from 5 to  
2      $10^5$  molecules.

1                    53.     A method as in claim 52, wherein the plurality consists of from 7 to  
2      $5 \times 10^4$  molecules.

1                    54.     A method as in any of claim 49, wherein the molecules comprise  
2     rapamycin molecules which have been derivatized with linking moieties and wherein the  
3     rapamycin molecules are covalently bound through the moieties to the backbone.

1                    55.     A method as in claim 54, wherein the linking moieties are bound to the  
2     rapamycin molecules at sites which do not sterically interfere with the active sites of  
3     rapamycin so that rapamycin retains its activity when attached to the backbone.

1                    56.     A method as in claim 54, wherein the linking moieties are bound to  
2     rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so  
3     that rapamycin activity is inhibited while the rapamycin remains attached to the backbone  
4     and restored when the rapamycin is released from the backbone.

1                    57.     A method as in claim 54, wherein the backbone degrades under  
2     preselected conditions to release the rapamycin molecules.

1                    58.     A method as in claim 54, wherein the linking moieties lyse under  
2     preselected conditions to release the rapamycin molecules from the backbone.

1                    59.     A method as in claim 54, wherein the backbone comprises a poly  
2     (amino acid).

1                    60.     A method as in claim 59, wherein the backbone is polyaspartate,  
2     wherein rapamycin is covalently attached via an ester linkage between a free carboxylic acid  
3     on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1                    61.     A method as in claim 59, wherein the backbone is polylysine, wherein  
2     rapamycin is covalently attached via a heterobifunctional linker between a free thiol on the  
3     lysine to a free hydroxyl at position 42 of rapamycin.

1                   62.     A method as in claim 59, wherein the backbone is polylysine, wherein  
2 rapamycin is covalently attached via an amide-ester linkage between a free amine on the  
3 lysine to a free hydroxyl at position 42 of rapamycin.

1                   63.     A method as in claim 59, wherein the backbone is polylysine, wherein  
2 rapamycin is covalently attached via a disulfide linkage through a free thiol introduced to the  
3 rapamycin.

1                   64.     A method as in claim 59, wherein the backbone comprises  
2 polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to the PEG  
3 by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1                   65.     A method for preparing a linked plurality of molecules which  
2 specifically bind to the mammalian target of rapamycin, said method comprising:  
3 polymerizing the molecules.

1                   66.     A method as in claim 65, wherein the plurality consists of from 3 to  
2  $10^6$  molecules.

1                   67.     A method as in claim 66, wherein the plurality consists of from 5 to  
2  $10^5$  molecules.

1                   68.     A method as in claim 67, wherein the plurality consists of from 7 to  
2  $5 \times 10^4$  molecules.

1                   69.     A method as in claim 65, wherein the molecules comprise rapamycin.

1                   70.     A method as in claim 69, wherein polymerizing comprises:  
2 derivatizing the rapamycin molecules with a polymerizable moiety; and  
3 polymerizing the polymerizable moieties to covalently bind the rapamycin  
4 molecules via the moieties.

1                   71.     A method as in claim 70, wherein the linking moieties are bound to the  
2 rapamycin molecules at sites which do not sterically interfere with the active sites of  
3 rapamycin so that rapamycin retains its activity when polymerized.

1                   72.     A method as in claim 70, wherein the linking moieties are bound to the  
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so  
3 that rapamycin activity is inhibited while the rapamycin remains polymerized and restored  
4 when the rapamycin is released.

1                   73.     A method as in claim 70, wherein the polymerized moieties lyse under  
2 preselected conditions.

1                   74.     A method as in claim 70, wherein the polymerized moieties comprise  
2 ascorbic acid attached to the rapamycin molecules via an ester linkage.

1                   75.     A method as in claim 70, wherein the polymerizable moiety comprises  
2 ascorbic acid.

1                   76.     A method for modifying an implantable prosthesis, said method  
2 comprising:  
3                   providing an implantable prosthesis having a surface; and  
4                   binding linked pluralities of molecules which specifically bind to the  
5 mammalian target of rapamycin (mTOR).

1                   77.     A method as in claim 77, wherein the implantable prosthesis comprises  
2 a vascular prosthesis or stent implantable in a blood vessel.

1                   78.     A method as in claim 77, wherein binding comprises covalently  
2 attaching linked pluralities of rapamycin to the surface.

1                   79.     A method as in claim 78, wherein binding comprises generating free  
2 amines on the surface and forming an amide linkage to a carboxy moiety in the linked  
3 pluralities of rapamycin.

1                   80.     A method as in claim 78, wherein the linked pluralities of rapamycin  
2 have from 3 to  $10^6$  molecules linked.

1                   81.     A method as in claim 79, wherein the linked pluralities of rapamycin  
2 have from 5 to  $10^5$  molecules linked.



1                   82.     A method as in claim 80, wherein the linked pluralities of rapamycin  
2     have from 7 to  $5 \times 10^4$  molecules linked.

1                   83.     A method as in any of claim 78, wherein the linked pluralities of  
2     rapamycin are linked via attachment to a backbone.

1                   84.     A method as in claim 83, wherein the molecules comprise rapamycin  
2     molecules which have been derivatized with linking moieties and wherein the rapamycin  
3     molecules are covalently bound through the moieties to the backbone.

1                   85.     A method as claim 84, wherein the linking moieties are bound to the  
2     rapamycin molecules at sites which do not sterically interfere with the active sites of  
3     rapamycin so that rapamycin retains its activity when attached to the backbone.

1                   86.     A method as in claim 84, wherein the linking moieties are bound to  
2     rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so  
3     that rapamycin activity is inhibited while the rapamycin remains attached to the backbone  
4     and restored when the rapamycin is released from the backbone.

1                   87.     A method as in claim 83, wherein the backbone degrades under  
2     preselected conditions to release the rapamycin molecules.

1                   88.     A method as in claim 83, wherein the linking moieties lyse under  
2     preselected conditions to replace the rapamycin molecules from the backbone.

1                   89.     A method as in claim 83, wherein the backbone comprises a poly  
2     (amino acid).

1                   90.     A method as in claim 89, wherein the backbone is polyaspartate,  
2     wherein rapamycin is covalently attached via an ester linkage between a free carboxylic acid  
3     on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1                   91.     A method as in claim 89, wherein the backbone is polylysine, wherein  
2     rapamycin is covalently attached via a heterobifunctional linker between a free thiol on the  
3     lysine to a free hydroxyl at position 42 of rapamycin.

1                    92.     A method as in claim 89, wherein the backbone is polylysine, wherein  
2 rapamycin is covalently attached via an amide-ester linkage between a free amine on the  
3 lysine to a free hydroxyl at position 42 of rapamycin.

1                    93.     A method as in claim 89, wherein the backbone is polylysine, wherein  
2 rapamycin is covalently attached via a disulfide linkage through a free thiol introduced to the  
3 rapamycin.

1                    94.     A method as in claim 83, wherein the backbone comprises  
2 polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to the PEG  
3 by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1                    95.     A method as in any of claim 78, wherein the molecules are  
2 polymerized.

1                    96.     A method as in claim 95, wherein the molecules comprise rapamycin  
2 molecules which have been derivatized with linking moieties and wherein the rapamycin  
3 molecules are polymerized through the linking moieties.

1                    97.     A method as in claim 96, wherein the linking moieties are bound to the  
2 rapamycin molecules at sites which do not sterically interfere with the active sites of  
3 rapamycin so that rapamycin retains its activity when polymerized.

1                    98.     A method as in claim 96, wherein the linking moieties are bound to the  
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so  
3 that rapamycin activity is inhibited while the rapamycin remains polymerized and restored  
4 when the rapamycin is released.

1                    99.     A method as in claim 96, wherein the linking moieties lyse under  
2 preselected conditions.

1                    100.    A method as in claim 96, wherein the linking moieties comprise  
2 ascorbic acid attached to the rapamycin molecules via an ester linkage.

1                    101.    A composition as in any of claim 1, further comprising an unlinked  
2 ascorbic acid moiety.